

Solid-Papillary Tumors of the Pancreas: Histopathology

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Summary

A solid-pseudopapillary tumor is an uncommon and "enigmatic" pancreatic neoplasm, and the term encompasses the two most conspicuous histological features: solid and pseudopapillary areas.

Grossly, it appears as a large solid, cystic or solid-cystic mass frequently having necrotic and hemorrhagic zones. Histologically, solid-pseudopapillary tumors are generally characterized by solid areas alternating with a pseudopapillary pattern, and cystic spaces which are the results of degenerative changes occurring in the solid neoplasm. Its immunohistochemical pattern is very distinctive and neoplastic cells are consistently vimentin-, CD10- and CD56-positive. Some cases express focal positivity for alpha-1-antitrypsin, alpha-1-antichymotrypsin, neuron-specific enolase and synaptophysin. Progesterone receptors are frequently present. Keratins are not expressed or are found only focally. Endocrine and pancreatic enzyme markers are absent; the origin of solid-pseudopapillary tumors has not yet been clarified. Many investigators favor the theory that solid-pseudopapillary tumors originate from multipotent primordial cells while others suggest an extra-pancreatic origin from genital ridge angle-related cells. Some controversy exists for both hypotheses. Solid-pseudopapillary tumors appear as a low malignancy tumor and only a small number of cases recur or develop metastases after

resection. No pathological factors were found to correlate with the prognosis. Some histological features have recently been suggested to be associated with aggressive behavior.

A solid-pseudopapillary tumor (SPT) is an uncommon and "enigmatic" pancreatic neoplasm, first observed in 1927 in a 19-year-old woman and first described by Frantz in 1959 [1, 2].

Over time, this tumor has been designated with various names such as: Frantz's tumor; solid and papillary tumor; papillary cystic tumor; solid-cystic tumor; solid, cystic and papillary epithelial neoplasm; benign or malignant papillary tumor of the pancreas, papillary epithelial neoplasm of pancreas in a child and adenocarcinoma of the pancreas in childhood [1, 3].

The term 'solid-cystic' was proposed because of the gross features of the tumor while the designations 'papillary-cystic' and 'solid-papillary' mainly relate to the most obvious histological pattern [3, 4]. However, since these terms do not exactly reflect what is observed either at the macroscopic or the microscopic level, WHO, in 1996, proposed the name 'solid-pseudopapillary tumor' [3, 5]. This term encompasses the two most conspicuous histological features: solid and pseudopapillary areas.

SPTs are very rare; in fact, they only constitute about 5% of cystic pancreatic

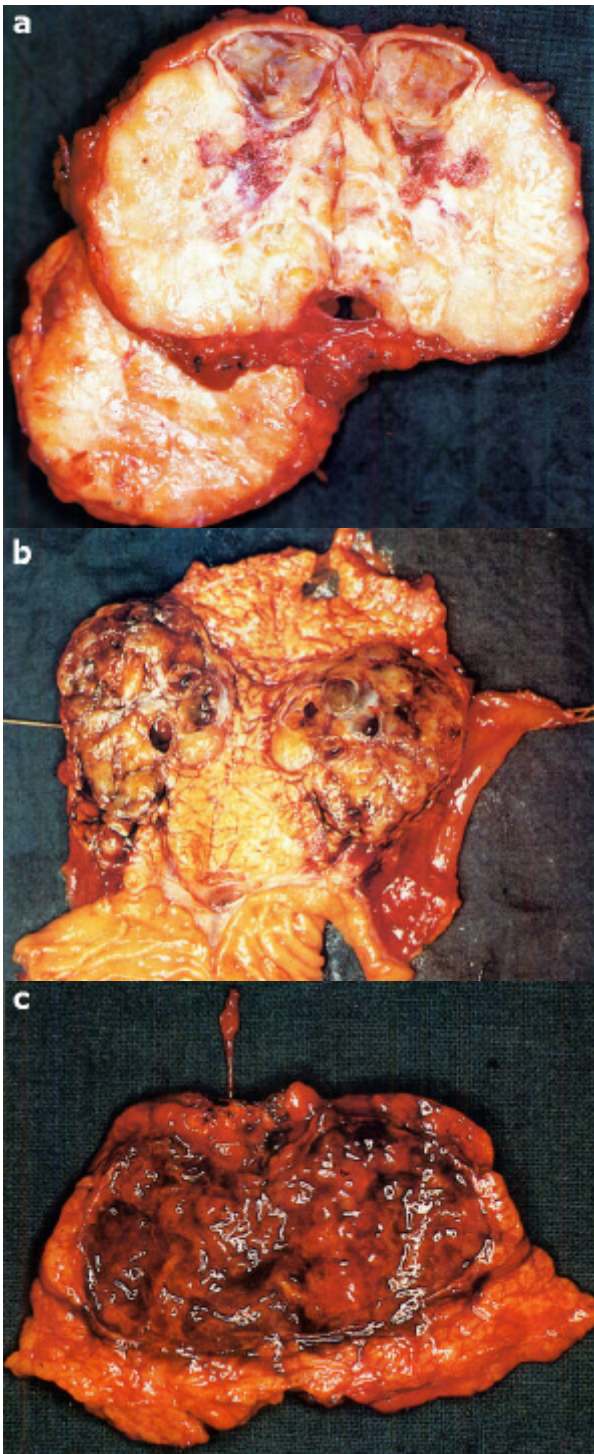


Figure 1. Solid-pseudopapillary tumor: on gross examination, the neoplasm reveals a solid, cystic, solid-cystic (a., b.) or hemorrhagic (c.) appearance. (The same images are presented in another contribution by the same authors, published in these Proceedings [29], in order to describe aspects not related to those reported here).

tumors and about 1-2% of exocrine pancreatic neoplasms [1, 2]. However, in recent years, SPTs have been identified with increasing

frequency due to better awareness of their existence, larger availability of immunohistochemical stains and retrospective studies in which cases which had not been identified correctly have been reported.

It is most common in women (82%) about 30 years of age but, occasionally, the tumor occurs in older women, men or children [4, 6].

SPTs can occur in every part of the pancreas but they are slightly more common in the tail [1, 7]. On gross examination, a solid, cystic, solid-cystic and/or hemorrhagic appearance may be possible. The size of the tumors ranges from as small as 1.5 to as large as 30 cm in diameter.

Grossly, it appears as a large and encapsulated mass, generally well-demarcated from the remaining pancreas. In fact, invasion of adjacent organs, such as the spleen or the duodenal wall, is rare.

Cut sections show the alternation of solid and yellowish areas with cystic, frequently necrotic and hemorrhagic zones (Figure 1ab). Occasionally, the hemorrhagic-cystic changes involve almost the entire tumoral tissue simulating a pancreatic hematoma (Figure 1c) [4, 7].

In smaller SPTs, there are often variable amounts of fibrosis, and cystic changes can be less prominent.

Rarely does the tumor have a double or extrapancreatic location [1, 4].

Histologically, SPT is generally characterized by solid areas which alternate with a pseudopapillary pattern (Figure 2), and cystic

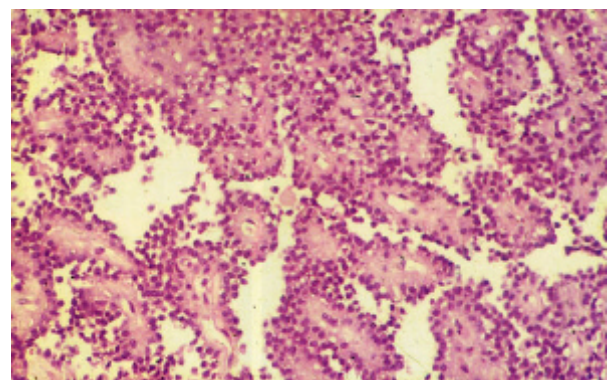


Figure 2. Solid-pseudopapillary tumor: histologically, the tumor displays a pseudopapillary pattern.

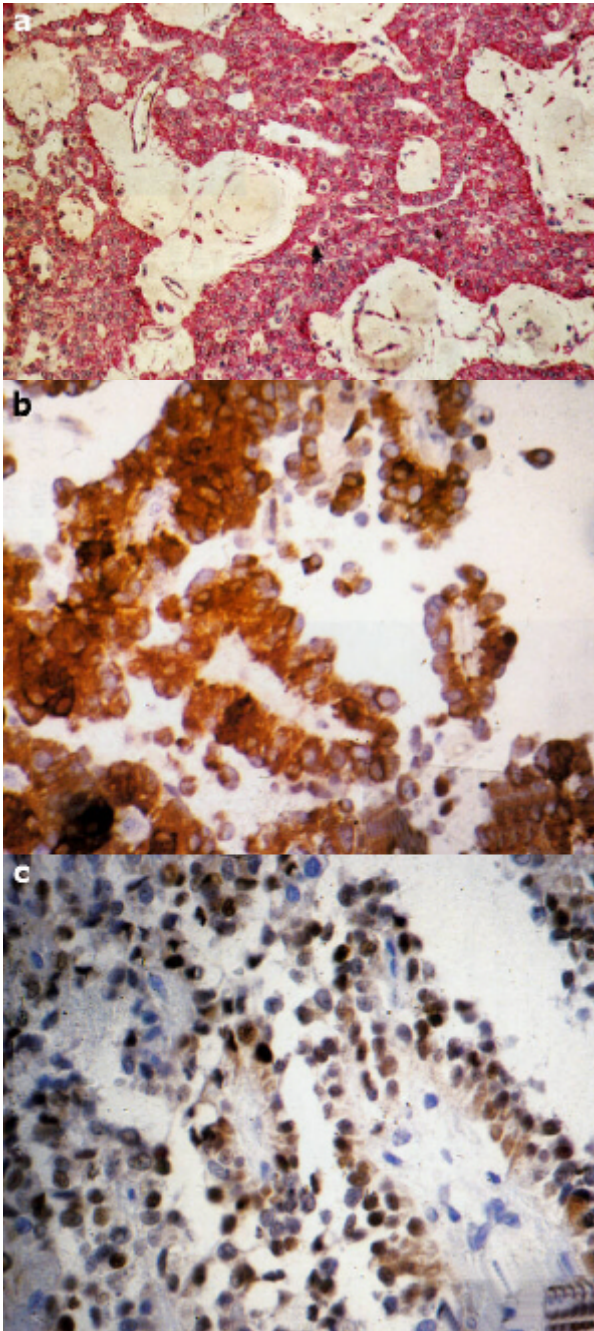


Figure 3. Solid-pseudopapillary tumor: tumor tissue with diffuse immunostaining for Vimentin (a.), neuron-specific enolase (NSE) (b.) and progesterone receptor (c.).

spaces which are the results of gradual degenerative changes occurring in the solid neoplasm.

Solid areas are formed by cords of small to medium sized, polygonal, monomorphous cells, separated by small vessels which exhibit a variable degree of perivascular collagen deposition.

Tumor cells present eosinophilic and vacuolar cytoplasm, around an often grooved ovoid nucleus, containing a nucleolus and dispersed chromatin.

Occasionally cells contain aggregates of hyaline, diastase resistant, PAS-positive cytoplasmic globules of varying size which are also sometimes located outside the cells.

Near the cystic spaces, accompanying the degenerative changes, it is possible to see aggregates of foamy histiocytes, cholesterol clefts, foreign body giant cells and hemorrhage.

The tumor tissue is usually well-demarcated from the normal pancreas by a fibrous capsule, although a separating layer of connective tissue may be missing. Occasionally, there is vessel invasion.

The mitotic index and Ki67 are usually low, emphasizing the low malignancy of the neoplasm [1, 4, 8].

Despite the fact that the phenotype of SPT does not resemble that of any of the normal epithelial cells of the pancreas, its immunohistochemical pattern is very distinctive. Neoplastic cells are consistently vimentin-positive (Figure 3a). Other consistently positive markers include alpha-1-antitrypsin and alpha-1-antichymotrypsin with parallel distribution of the hyaline globules [1, 9, 10]. Some cases express focal positivity for neuron-specific enolase (NSE) (Figure 3b) and synaptophysin [11, 12]. There is also a frequent presence of progesterone receptors (Figure 3c) [13, 14] and recently a strong positivity for CD10 and CD56 has been reported [15].

Keratins are not expressed or are found only focally. Endocrine and pancreatic enzyme markers are absent [4].

Epithelial membrane antigen (EMA) and chromogranin are also not expressed.

The differential diagnosis of SPT includes acinar tumors, pancreatoblastoma, and endocrine tumors, adenocarcinoma. However, the immunohistochemical pattern of SPTs is distinctive and differs from that of other primary pancreatic tumors which should be considered in the differential diagnosis [3, 4].

The molecular profile is different from the generic changes involved in conventional pancreatic carcinomas [11, 16]. In SPT, alteration of the adenomatous polyposis coli (APC)/beta catenin pathway and deregulated expression of cell cycle-associated protein as over-expression of cyclin D1 and cyclin D3 can be observed. There is also up-regulation of cyclin-dependent Kinase inhibitors: p21 and p27 [17]. K-ras mutation and p53 mutation were not observed [3, 18].

The origin of SPTs has not yet been clarified. Almost all reports discuss its origin in detail but the line of cellular differentiation remains uncertain.

SPTs are classified and are generally held to be epithelial neoplasms but immunohistochemical patterns suggest that SPTs cannot be regarded as purely epithelial neoplasms [8]. In fact, cytokeratin expression, usually associated with epithelial differentiation, is rare (less than 30%) or absent in most cases, and markers of acinar differentiation (trypsin/chymotrypsin) and glycoprotein markers of ductal differentiation are often negative [19, 20].

However, SPTs cannot even be regarded as a purely neuroendocrine neoplasm because the presence of neuroendocrine markers is not significant (chromogranin A is not detected, synaptophysin has a patchy immunoreactivity in 22% and NSE is strongly positive in more than 90% but without a certain significance) [4, 21].

Due to the cell characteristics of SPTs, different origin hypotheses have been postulated. Many investigators favor the theory that SPTs originate from multipotent primordial cells [15, 22, 23] while others suggest an extra-pancreatic origin from genital ridge angle-related cells [24]. Some controversy exists for both hypotheses. We could consider their origin to be from pluripotent embryonic cells of the pancreas with multipotential differentiation [3, 25]. In fact, on the one hand, SPTs express epithelial, mesenchymal, exocrine and endocrine features, and their cells may originate from the ductular-centroacinar cell compartment

which, during embryogenesis, is thought to give rise to exocrine and endocrine cells. However, on the other hand, there is no evidence of clear-cut terminal differentiation to either acinar or endocrine cells; the cytological features and the low proliferative activity and malignancy are not consistent with a stem cell origin and, finally, the strongly sex-linked occurrence is not in keeping with a stem cell origin [10, 13, 16, 26].

We can also consider the origin from genital ridges of ovarian-related cells attached to pancreatic tissue during early embryogenesis. In fact, on the one hand, immunohistochemical stains are not consistent with those of any pancreatic cells and there are similarities between SPTs and ovarian surface cells. Thus, SPTs might originate from genital ridge-related cells which were incorporated into the pancreas during organogenesis. However, on the other hand, it is not possible to identify an ovarian cell which exactly corresponds to the immunohistochemical pattern of SPT cells and there are no ovarian tumors having a strong similarity to SPTs [27]. Moreover, SPTs also occur in men without sex hormone abnormalities.

Therefore, the question is still open and "enigmatic".

Generally, SPTs appear as low malignancy tumors and only a small number of cases recur or develop metastases after resection [4]. In fact, the follow-up of a large number of cases has shown that the majority of SPTs are benign, but the benign category of SPTs is not included [4].

In fact, SPTs have been differentiated by the WHO classification into:

1. solid-pseudopapillary neoplasms with borderline malignant potential;
2. solid-pseudopapillary carcinomas.

Criteria which distinguish potentially malignant tumors and which are classified as 'SPT carcinoma' are:

1. angioinvasion;
2. perineural invasion;

3. deep invasion of the surrounding pancreatic parenchyma.

Generally, SPTs appear as low malignancy tumors and only a small number of cases recur or develop metastases after resection. However, even tumors without these criteria of malignancy may give rise to metastases and therefore, in spite of their features of benignity, they are classified as 'SPT with borderline malignant potential' [10].

No pathological factors including mitotic rate, nuclear pleomorphism and vascular invasion were found to correlate with the prognosis. Recently, some histological features such as extensive necrosis, nuclear atypia, high mitotic rate and sarcomatoid areas have been suggested to be associated with aggressive behavior [28].

Keywords Pancreas; Pancreatic Neoplasms

Abbreviations APC: adenomatous polyposis coli; NSE: neuron-specific enolase; SPT: solid-pseudopapillary tumor

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